REMARKS/ARGUMENTS.

Claims 3, 5, 7, 10-15, 18, 19, 32 and 34-36 were already withdrawn from consideration.

Claims 8 and 9, plus claims 20 and 22-28 are now also withdrawn.

Hence, claims 1-2, 4, 6, 16-17, 21 and 29-31 are currently pending in this application.

1. 35 USC §103 (OBVIOUSNESS) REJECTIONS.

1.1 Sahagan.

Claims 1-7, 12, 14-19, 21 and 29-33 stand rejected as lacking an inventive step over Sahagan (EP 1088550 A1).

The Examiner states that:

> "It would have been prima facie (obvious) to one of ordinary skill in the art to substitute ^{18}F at the 4 position of the phenyl ring in order to form an isotopically-labeled compound useful in drug and/or substrate distribution assays such as PET or SPECT."

In response, applicants firstly point out that the teaching of Sahagan is, in reality, rather different to that suggested by the Examiner. Thus, at page 10 lines 27-32, Sahagan states:

> "The subject invention also relates to a method of treatment which relates to isotopically-labeled compounds, which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds relating to

> the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively."

Those examples of isotopes cited by Sahagan thus refer specifically to the method of treatment, not imaging.

Applicants secondly point out that Sahagan also teaches (page 10 lines 34-36) that:

> "Certain isotopically compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. "

Thus, Sahagan teaches very clearly that only "certain isotopically-labelled compounds" [emphasis added] are useful for drug and/or substrate tissue distribution assays. It is thus inaccurate for the Examiner to suggest that all the isotopes taught by Sagan at page 10 lines 30 - 32 are suitable for use in such assays.

Furthermore, the person skilled in the art would understand the term 'assay' to have its conventional meaning, eg:

> "The determination of the content or strength of a substance."
> [Concise Oxford Dictionary, 8th Edition, Clarendon Press, Oxford (1992)].

Thus, an assay refers to generating a number representative of the amount of substance. In the context of Sahagan, that means measuring the amount of the drug in different organs/tissues. The only specific isotopes mentioned in this context by Sahagan are ^{3}H (i.e. tritium) and ^{14}C. The person skilled in the art would immediately recognize that Sahagan is here talking about standard drug biodistribution studies, not medical imaging. Such drug

biodistribution studies generate a number, but do not generate an image of the organ or tissue involved.

Applicants respectfully point out that PET and SPECT are methods of radiopharmaceutical *in vivo* medical imaging in which 2-dimensional or 3-dimensional images of an organ or tissue are generated. They are not "distribution assays". Thus, PET and SPECT are very different from 'tissue biodistribution assays'. It is therefore inaccurate for the Examiner to equate the two – and the Examiner cannot ascribe a teaching to Sahagan which cannot be identified within the document itself.

In summary, Sahagan teaches methods of treatment using various labeled compounds and drug biodistribution studies. Sahagan is silent on medical imaging, let alone the PET and SPECT imaging of the present claims.

The Examiner argues that the person skilled in the art would be motivated to substitute ^{18}F to form an isotopically-labelled compound useful in drug and/or substrate distribution assays. Even assuming the person skilled in the art were indeed motivated to carry out such "drug and/or substrate distribution assays", then ^{18}F would not be a plausible isotope. Thus, ^{18}F has a half-life of 109 minutes, and hence would provide a significant radiation dose whilst tissues were dissected in order to count the radioactivity present and hence carry out the assay. In addition, the short half-life would place considerable time pressure on any study – since the radioactive decay would cause both rapid loss of signal and problems with the variation in the counting statistics over the time course of the experiment. Much more appropriate would be the ^{3}H (tritium) and ^{14}C isotopes actually taught in this regard by Sahagan, which have substantially longer half-lives (12.3 years and 5760 years respectively), so are much more suitable for such studies. Hence, if Sahagan is properly construed, in the absence of the teaching of the present invention, and in the light of the common general knowledge of the person skilled in the art, any motivation it provides towards tissue distribution assays teaches towards ^{3}H and/or ^{14}C, not ^{18}F. Thus, the Examiner's alleged motivation in this regard does not actually exist.

The obviousness objection to claim 1 based on Sahagan should therefore be withdrawn. The remaining claims all either depend on or refer to claim 1. Hence, they are believed to be non-obvious for the same reasons.

The obviousness rejection to claims 1-7, 12, 24-19, 21 and 29-33 based on Sahagan should therefore be withdrawn in its entirety.

1.2 Sahagan and Wilbur.

Claims 1-7, 12, 14-19, 21 and 29-33 stand rejected as lacking an inventive step over Sahagan in view of Wilbur [Bioconj.Chem., 3(6), 433-470 (1992)].

The Examiner argues that the general concept of changing the non-radioactive isotope to a radioisotope for PET/SPECT imaging comes from Sahagan, and that the specific ^{123}I substituent is provided by Wilbur. Applicants respectfully suggest that this logic is flawed. Thus, applicants stress that the teaching of Sahagan on 'tissue distribution studies" cannot be equated to PET/SPECT medical imaging. See (1.1) above.

Hence, the alleged motivation to combine does not actually exist.

In addition, Sahagan teaches very clearly that the compounds therein can be isotopically labeled by exchanging an existing atom of the structure – see [0043] therein at page 10. The molecule suggested by the Examiner on page 7 contains an iodine substituent/atom, which is not taught by Sahagan. The structure therefore contradicts the teaching of Sahagan itself, and hence should be withdrawn.

In addition, Wilbur states (page 434 right hand column, 3rd paragraph) that the method therein refers to proteins and might be applicable to peptides of less than 50 amino acids. Thus, Wilbur refers to radiolabelling proteins and peptides. Wilbur is silent on the radiolabelling of non-peptide small molecules such as the metalloproteinase inhibitors of

Sahagan. The person skilled in the art could therefore have no motivation to apply Wilbur to Sahagan, since Sahagan refers to molecules outside the scope of the molecules radiolabelled by Wilbur. The two references are thus not properly combinable.

For these reasons, the obviousness rejection based on the combination Sahagan/Wilbur should therefore also be withdrawn.

1.3 Sahagan, Wilbur and Fruchtel.

Claim 33 stands rejected as lacking an inventive step over Sahagan in view of Wilbur, and in further view of Fruchtel [Angew.Chem.Int.Ed.Engl., 35, 17-42 (1996)].

The Examiner argues here that the compounds, methods and kits are already obvious from Sahagan/Wilbur, and that the additional feature of claim 33 is available in an obvious manner from Fructel.

Applicants contend that this argument is no longer valid, since claims 1-7, 12, 14-19 and 29-32 are in fact non-obvious over the prior art (see above). The obviousness objection to claim 33 should therefore be withdrawn.

2. Double Patenting.

Claims 1-7, 12, 14-19, 21 and 29-33 are provisionally rejected under the doctrine of obvious-type double patenting, as being unpatentable over claims 1-29 of co-pending US patent application 10/544945. In response, Applicants submit that a terminal disclaimer will be filed once the instant application is indicated to be allowable.

CONCLUSION.

Upon entry of this Amendment, claims 1-2, 4, 6, 16-17, 21 and 29-31 remain pending. Applicants submit that all outstanding issues have been addressed, and that claims 1-2, 4, 6, 16-17, 21 and 29-31 are in condition for allowance, which action is earnestly solicited.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

Respectfully submitted,

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